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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,346	03/16/2001	David Nanus	ARG-912-C1	1693

23565 7590 02/10/2004

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,346	NANUS, DAVID	
	Examin r	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-7,9-26 and 28-31 is/are rejected.

7)☐ Claim(s) 8,27 and 32-34 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of sections of Title 35, U.S. Code not found in this action can be found in a previous action.

Claims 6 and 8 have been amended. Claims 1-34 are pending and under consideration.

New Grounds of Rejection

Claims 1-17, 19-25, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134, pp. 99-104, reference of the IDS filed June 16, 2003) in view of Parthasarathy et al (Cancer Letters, 1998, Vol. 134, pp. 121-128) and Regazzi et al (Clinical Pharmokinetics, 1997, Vol. 32, pp. 382-402).

Claim 1 is drawn to a method of inhibiting the growth of cancer cells comprising exposing cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid wherein said retinoid is associated with lipid carrier particles. claim 2 embodies the method of claim 1 wherein the retinoid is retinoic acid. Claim 3 embodies the method of claim 2 wherein the retinoic acid is all-trans retinoic acid. Claim 17 embodies the method of claim 3 wherein the amount of all-trans retinoic acid is about 15-300 mg/m2. Claim 4 embodies the method of claim 1 wherein the lipid carrier particles comprising all-trans retinoic acid, lipid and a triglyceride, wherein a molar ratio of retinoid to lipid is at least about 15:85, the triglyceride is at least 15% by weight of the composition, wherein said composition is stable in an aqueous environment. Claim 29 embodies the method of claim 4 wherein the cancer is a renal cancer. Claim 7 embodies the method of claim 1 wherein the cancer is a renal cancer. Claim 5 embodies the method of claim 1 comprising administering said retinoid composition by intravenous infusion. Claim 6 embodies the method of claim 1 wherein the composition comprising at least one interferon and a retinoid is administered at a frequency from daily to about 3 out of 7 days a week.

Claim 8 is drawn to a method of inhibiting the growth of cancer cells comprising co-timely exposing cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a therapeutically effective amount of a retinoid, wherein said retinoid is associated with lipid carrier particles. Claim 10 and 11 embody the methods of claims 1 and 8, respectively, wherein the cancer is selected from the group consisting of renal

cancer, breast cancer, head cancer and neck cancer. Claims 30 and 31 embody the methods of claims 10 and 11, respectively, wherein the cancer is a renal cancer. Claims 12 and 13 embody the methods of claims 1 and 8 respectively, wherein the cancerous cells are exposed in vivo. Claims 14 and 19 embody the methods of claims 1 and 8, respectively, wherein the interferon is selected from the group consisting of alpha, beta and gamma interferon. Claims 15 and 20 specify that the interferon of claims 14 and 19 is alpha interferon. Claims 16 and 21 embody the methods of claims 15and 20, respectively, wherein the alpha-interferon is administered in an amount of about 1 to about 25 million IU.

Claim 9 is drawn to a therapeutic treatment kit for the treatment of cancer comprising interferon, all-trans retinoic acid and instructional materials for the combined use of said all-trans retinoic acid and interferon.

Claim 22 is drawn to a method of inhibiting the growth of cancer cells, wherein the cancer cells are selected from the group consisting of renal, head, neck and breast cancer cells, comprising exposing said cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid, wherein the retinoid is all-trans retinoic acid and is associated with lipid carrier particles. Claim 23 embodies the method of claim 22 wherein the interferon is selected from the group consisting of alpha, beta and gamma interferon. Claim 24 specifies that the interferon of claim 23 is alpha interferon. claim 25 embodies the method of claim 24, wherein the alpha interferon is administer in an amount of about 1 to about 25 million IU. Claim 26 embodies the method of claim 22 wherein the amount of all-trans retinoic acid is about 15-300 mg/m2.

Claim 28 is drawn to a method of inhibiting the growth of cancer cells, wherein the cancer cells are selected from the group consisting of renal, head, neck and breast cancer cells comprising exposing said cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid, wherein the retinoid is all-trans retinoic acid and is associated with lipid carrier particle and the at least one interferon is alpha interferon.

Bonhomme-Faivre et al teach the treatment of patients with advanced renal cancer comprising the administration of ATRA at 100 mg/m2/day concomitantly with IFN-alpha (9-18 million IU/m2), three days a week, thus fulfilling the specific embodiment of claim 6 drawn to daily to about 3 out of 7 days per week, the specific embodiments of claims 16, 21 and 25 drawn

to the administration of alpha interferon in an amount of about 1 to about 25 million IU, and the specific embodiments of claims 17 and 26 drawn to the administration of all-trans retinoic acid in an amount of about 15-300 mg/m2. Bonhomme-Faivre et al teach that ATRA binds to serum albumin in plasma where it is rapidly taken up by the liver and metabolized (page 99, second column, last paragraph). Bonhomme-Faivre et al teach that the combination of ATRA and IFN possess an enhanced anti-proliferative effect on some renal cancer cell lines (page 100, first column, lines 27-31). Bonhomme-Faivre et al teach that the plasma concentrations of ATRA were relatively low in the patients that were studied (page 102, second column, lines 6-7 under the heading "Discussion"). Bonhomme-Faivre et al teach that IFN increased peak plasma levels of ATRA and reduced the clearance rate of ATRA (page 102, first column, lines 17-20) by means of depressing the hepatic cytochrome P450 drug metabolizing system and enhances in vivo ATRA effects (page 100, first column, lines 24-27 and page 103, first column, lines 14-19). Bonhomme-Faivre et al teach that administration of ATRA on an intermittent basis allows for the circumvention of the elevated plasma clearance rate of ATRA, but may be associated with lower clinical efficacy (page 103, first column, lines 20-26). Bonhomme-Faivre et al teach co-administration of IFN and ATRA should be expected to increase peak plasma levels of ATRA and decrease clearance of ATRA (page 103, first column, lines 27-29). Bonhomme-Faivre et al do not teach the intravenous administration of ATRA associated with lipid carrier particles.

Parthasarathy et al teach that encapsulation of ATRA in lipid vesicles reduced in vitro toxicity and retains the full biological activity of the ATRA. Parthasarathy et al teach that encapsulation of ATRA in liposomes protects the drug from catabolic enzymes and decreases exposure of normal tissues to retinoid (page 125, second column, lines 19-26) and thus results in the higher exposure of target cells to the active form of ATRA for longer periods (page 126, second column, last sentence of the last full paragraph). Parthasarathy et al teach that accumulation of liposomes in reticuloendothelial organs, such as the liver and spleen can be circumvented by the use of cationic liposomes, (such as the liposomes formulated by diphosphatidyl palmitoylcholine and stearylamine in a 9:1 ratio, which when converted to a molar ratio corresponds to the limitations of claim 4) rather than anionic liposomes (page 125, second column, lines 17-19 of the last paragraph). Parthasarathy et al teach that orally administered ATRA not encapsulated in a liposome accumulates predominately in hepatocytes

(page 125-126, bridging sentence and page 126, second column, lines 1-5 of the first full paragraph) and that only 20-25% of lipsosomal ATRA administered intravenously accumulates in the liver and Kupffer cells.

Regazzi et al teach a new formulation of all-trans retinoic acid (tretinoin) developed for intravenous administration to provide pharmacological advantages over the oral formulation of tretinoin. Regazzi et al teach that animal treated long term with intravenous liposomal tretinoin metabolized retinoic acid to a lesser extent than animals treated with free tretinoin. Regazzi et al teach that lipid formulation bypasses the clearance mechanism which evolves in the liver of patients treated with oral tretinoin. Regazzi et al conclude that the liposomal formulation should not result in the same relapse rate which has been demonstrated in clinical trials with oral tretinoin administration, and should decrease the direct exposure of he drug during circulation to concentrations below the orally administered toxic dose resulting in less serve side effects (page 398-399, bridging paragraph).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer the liposomal encapsulated ATRA of Parthasarathy et al in place of free ATRA in the method taught by Bonhomme-Faivre et al . It would also have been prima facie obvious to package both liposomal encapsulated ATRA and interferon alpha in a kit for the convenience of administration to patients having renal cell carcinoma. One of skill in the art would have been motivated to do so by the teachings of both Parthasarathy et al and Regazzi et al on the decreased toxicity, and decreased metabolic clearance associated with liposomal ATRA versus free ATRA. One of skill in the art would be motivated to reduce hepatic accumulation and clearance in order to provide more of the administered dose to the target tissue.

Claims 1-17, 19-25, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134, pp. 99-104) and Parthasarathy et al (Cancer Letters, 1998, Vol. 134, pp. 121-128) and Regazzi et al (Clinical Pharmacokinetics, 1997, Vol. 32, pp. 382-402).as applied to claims 1-17, 19-25, 28-31 above, and further in view of Lippman et al (International Journal of Cancer, 1997, Vol. 70, pp. 481-483, reference of the IDS filed June 16, 2003) and Parthasarathy et al (Cancer Chemother Pharmacol, 1994, vol. 34, pp. 527-534).

Claims 10, 11, 22 and 28 recite the specific embodiments of head and neck cancer.

The combination of Bonhomme-Faivre et al, Parthasarathy et al (1998) and Ragazzi et al render obvious a method of treating renal cell cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha for the reasons set forth above. The combination does not render obvious a method of treating head and neck cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha.

Lippman et al teach a method for treating squamous cell carcinoma comprising the administration of 13-cis-retinoic acid and IFN (interferon alpha). Lippman et al teach that the largest disease group in the phase II clinical study were head/neck and skin cancers, and that a 50% response rate was attained in these two major disease groups (page 481, first column, lines 23-28).

Parthasarathy et al (1994) teach that liposomes formulated with dipalmitoylphsohatidycholine and stearylamine showed the optimal combination of low toxicity to red blood cells and effective delivery to target cells (page 530, second column, lines 6-11). Parthasarathy et al teach that said liposomes effective delivered 5600 pmol ATRA/mg protein in MDA 886Ln cells. (page 531, second column, lines 9-14). MDA 886Ln cells were derived from a metastatic lesion of squamous cell carcinoma of the larynx (page 528, first sentence under the heading of "Cell culture"). Parthasarathy et al teach that encapsulating retinoids may provide a means for delivering said retinoid without the resulting toxicity, sequester the drug as particles at tumor locations, protect the drug from rapid metabolism, amplify its therapeutic effect, and improve the solubility of lipophilic drugs such as retinoids (page 528, first column, lines 3-9)

It would have been prima facie obvious to one of skill in the art at the time the invention was made to substitute liposomal ATRA for the free 13-cis-retinoic acid in the method of treating head and neck cancers as taught by Lippman et al. One of skill in the art would be motivated to do so by the teachings of Parthasarathy et al (1994) on the high level of ATRA delivered to SCC cells by means of liposomal encapsulated proteins, and on the advantages associated with the use of liposomal retinoids which include decreased toxicity, decreased hepatic clearance and the sequestering of liposomal particles at the tumor site. One of skill in the art would be motivated to increase the local concentration of ATRA at the tumor site and decrease hepatic uptake and clearance in order to provide a higher dose of ATRA to the tumor

cells without increasing the administered dose, and thus decreasing the side effects associated with ATRA administration.

Claims 1-17, 19-25, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134, pp. 99-104) and Parthasarathy et al (Cancer Letters, 1998, Vol. 134, pp. 121-128) and Regazzi et al (Clinical Pharmacokinetics, 1997, Vol. 32, pp. 382-402) as applied to claims 1-17, 19-25, 28-31 above, and further in view of Marth et al (Journal of the National Cancer Institute, 1986, vol. 77, pp. 1197-1202, reference of the IDS filed June 16, 2003) and Parthasarathy et al (Cancer Chemother Pharmacol, 1994, vol. 34, pp. 527-534).

Claims 10, 11, 22 and 28 recite the specific embodiments of breast cancer. The combination of Bonhomme-Faivre et al, Parthasarathy et al (1998) and Ragazzi et al render obvious a method of treating renal cell cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha for the reasons set forth above. The combination does not render obvious a method of treating breast cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha.

Parthasarathy et al teach that encapsulating retinoids may provide a means for delivering said retinoid without the resulting toxicity, sequester the drug as particles at tumor locations, protect the drug from rapid metabolism, amplify its therapeutic effect, and improve the solubility of lipophilic drugs such as retinoids (page 528, first column, lines 3-9).

Marth et al teach that IFN-alpha and all-trans retinoic acid exerted synergistic antiproliferative effects on culture breast cancer cells (Figure 1).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to treat breast cancer with liposomal ATRA and IFN-alpha. One of skill in the art would be motivated to do so by the teachings of Parthasarathy et al (1994) on the advantages associated with the use of liposomal retinoids which include decreased toxicity, decreased hepatic clearance and the sequestering of liposomal particles at the tumor site. One of skill in the art would be motivated to increase the local concentration of ATRA at the tumor site and decrease hepatic uptake and clearance in order to provide a higher dose of ATRA to the tumor cells without increasing the administered dose, and thus decreasing the side effects associated

with ATRA administration. One of skill in the art would be motivated to combine ATRA and IFN-alpha in a treatment of breast cancer because the two agent exert a synergistic effect on cultured breast cancer cells.

Claims 8, 27, 32-34 are objected to for being dependent on rejected base claims.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

Karen A. Canella

Karen A. Canella, Ph.D.
Primary Examiner, Group 1642
01/14/04